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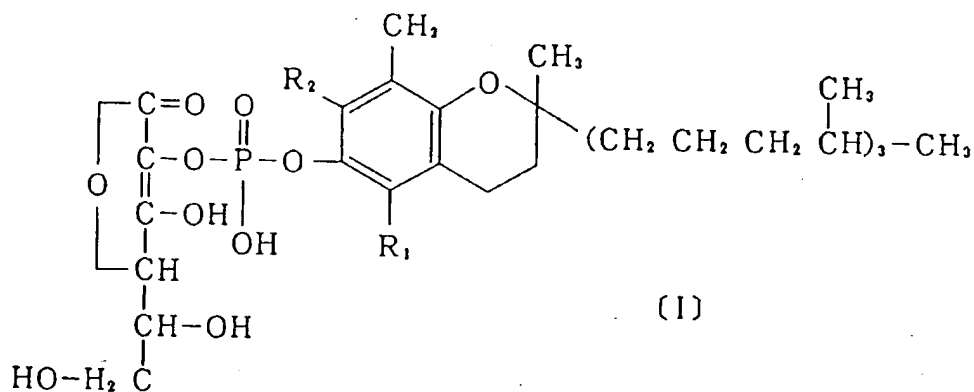
(71) Applicant : **Senju Pharmaceutical Co., Ltd.**  
5-8, Hiranomachi 2-chome,  
Chuo-Ku  
Osaka-shi, Osaka 541 (JP)

(72) Inventor : **Yoshida, Shoji**  
11-15, Kurakuen-sanban-cho  
Nishinomiya, Hyogo 662 (JP)  
Inventor : **Kawahira, Osamu**  
170-8, Otori-minami-machi 2-cho  
Sakai, Osaka 588 (JP)  
Inventor : **Ogata, Kazumi**  
8B-701, Kamishinden 4-chome  
Toyonaka, Osaka 565 (JP)

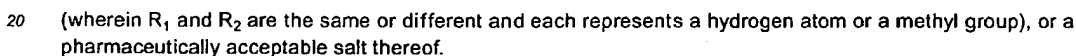
(74) Representative : **Burford, Anthony Frederick**  
W.H. Beck, Greener & Co.  
7 Stone Buildings  
Lincoln's Inn  
London WC2A 3SZ (GB)

(54) Topical antipruritic composition containing a phosphonic acid diester compound.

(57) Phosphoric acid diester compounds of the following formula (I) and pharmacologically acceptable salts thereof are used in a topical dosage form to contact a focus of pruritus to provide an antipruritic effect :



(wherein R<sub>1</sub> and R<sub>2</sub> are the same or different and each represents a hydrogen atom or a methyl group).



Reference in this application to compounds of formula (I) includes the free compounds and pharmacologically acceptable salts thereof unless another meaning is clear from the context. The salts include alkali metal salts, such as sodium salts and potassium salts, and alkaline earth metal salts, such as calcium salts and magnesium salts.

35 The Inventors have found that compounds of formula (I) exhibit remarkable efficacy, when topically administered at a certain concentration in the skin itch which is frequently encountered in diabetes and liver disorder as well as in senile pruritus. This invention has been developed on the basis of the above finding.

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(I)

Detailed description: The chemical structure (I) consists of a benzodioxane ring system. The benzene ring has substituents R<sub>1</sub> and R<sub>2</sub>. The dioxane ring has a methyl group (CH<sub>3</sub>) at the 2-position and a long alkyl chain at the 3-position, represented as (CH<sub>2</sub> CH<sub>2</sub> CH<sub>2</sub> CH(CH<sub>3</sub>))<sub>3</sub>-CH<sub>3</sub>. A phosphate group is attached to the benzene ring at the 4-position, which is linked to a sugar moiety. The sugar moiety is a ribose derivative with a carboxylic acid group at the 2-position and a hydroxyl group at the 3-position. The ribose is linked to a hydroxymethyl group (HO-H<sub>2</sub>C) at the 4-position.

(wherein  $R_1$  and  $R_2$  are the same or different and each represents a hydrogen atom or a methyl group).

The compounds of formula (I) can be incorporated either singly or in combination as necessary.

The antipruritic compounds of this invention are preferably used in an ointment form or as a water-based liquid preparation. The preferred water-based liquid preparation is an aqueous spray. In the manufacture of such preparations, a variety of conventional additives such as excipients, binders, thickeners, dispersing agents, reabsorption promoters, buffers, surfactants, preservatives, isotonicizing agents, stabilizers and pH control agents can be selectively employed.

The compounds of formula (I) are advantageously incorporated in an antipruritic product in such a manner that they may contact the focus of pruritus at a concentration of 0.01 - 5 (w/w) %. Below this concentration range, insufficient efficacy can be expected, while usage at any concentration over the range is not rewarded with enhanced efficacy.

The concentration of the compounds of formula (I) in the final dosage form may be 0.01 - 5 (w/w) %, preferably 0.05 - 2 (w/w) %, for an ointment or a cream, and 0.01 - 5 (w/w) %, preferably 0.05 - 2 (w/w) %, for an aqueous spray.

Unless contrary to the object of this invention, the pharmaceutical composition of this invention may be supplemented with other medicinally active substances such as antihistaminics, menthol, and camphor.

The following examples are further illustrative of this invention.

#### Preparation Example 1 Ointment

L-Ascorbyl DL- $\alpha$ -tocopheryl phosphate potassium	1.0 g
Hydrophilic ointment base	to 100 g

The above materials are mixed to provide an ointment.

#### Preparation Example 2: Gel

L-Ascorbyl DL- $\alpha$ -tocopheryl phosphate potassium	0.5 g
1-Menthol	0.5 g
Carbopol	1.0 g
Triethanolamine	q.s.
Ethanol	30 ml
Sterilized purified water	to 100 ml
Adjusted to pH 7.0	

#### Preparation Example 3: Aqueous sol

L-Ascorbyl DL- $\alpha$ -tocopheryl phosphate potassium	0.5 g
Glycerin	1.0 g
Propylene glycol	1.5 g
Ethanol	30 ml
Sterilized purified water	to 100 ml

#### Example 1:

A 55-year-old man presenting with eczema accompanied by itchy sensation in the abdominal and dorsal regions due to hepatic disorder was topically treated with the drug obtained in Preparation Example 1 for 2 weeks. As a result, not only pruritus but also eczema healed almost completely.



10. A use according to any one of Claims 7 to 9, wherein the medicament contains 0.01 - 5 (w/w) % of the said compound or salt thereof.
- 5 11. A use according to any one of Claims 7 to 10, wherein the said compound is L-ascorbyl DL- $\alpha$ -tocopheryl phosphoric acid or a salt thereof.

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## EUROPEAN SEARCH REPORT

Application Number  
EP 95 30 2199

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
D,X	EP-A-0 565 007 (SENJU PHARMACEUTICAL CO.) 13 October 1993 * the whole document *	1-3,7,8, 10,11	A61K31/665
X	EP-A-0 236 120 (SENJU SEIYAKU) 9 September 1987 * the whole document *	1,2,4,5	
D,X	PATENT ABSTRACTS OF JAPAN vol. 11 no. 371 (C-462), 3 December 1987 & JP-A-62 145019 (SENJIYU SEIYAKU) 29 June 1987, * abstract *	1,3,4	
D,X	EP-A-0 127 471 (SENJU SEIYAKU) 5 December 1984 * the whole document *	1-3,5	
X	DIALOG FILE SUPPLIER: FILE 129 PHIND: AN=00370992, 4 August 1993 * the whole document *	9,11	
A	J. SOC. COSMET. CHEM., vol. 38, 1987 pages 333-339, K. TOJO ET AL. 'BIOCONVERSION OF A PROVITAMIN TO VITAMINS C AND E IN SKIN' * the whole document *	1-11	TECHNICAL FIELDS SEARCHED (Int.Cl.6) A61K
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 25 July 1995	Examiner Hoff, P
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons A : member of the same patent family, corresponding document			

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